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SCULLY SCOTT MURPHY & PRESSER, PC
400 GARDEN CITY PLAZA
SUITE 300
GARDEN CITY, NY 11530

EXAMINER	
CHANDRAKUMAR, NIZAL S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/544,237	MOLINER ET AL.	
	Examiner	Art Unit	
	NIZAL S. CHANDRAKUMAR	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17 and 34-39* is/are pending in the application.

4a) Of the above claim(s) *9-19 and 34-38* is/are withdrawn from consideration.

5)☒ Claim(s) *39* is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :09/29/2005, 02/21/2006,03/26/2007, 06/04/2007,09/13/2007.

DETAILED ACTION

This application is a 371 of PCT/EP04/10882 09/29/2004

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-8 and 39 in the reply filed on 02/15/2008 is acknowledged. The traversal is on the ground(s) that Groups I, II and III are linked by a special technical feature as to form a venereal inventive concept. This is not found persuasive because for the reasons of record. The special technical feature is not a contribution over prior art because it is shown in the reference cited.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-17, 34-39 are pending.

Claims 9-17 and 34-38 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claims. Applicant timely traversed the restriction (election) requirement in the reply filed on 02/15/2008.

This application contains claim9-17 and 34-38 drawn to an invention nonelected with traverse in the reply filed on 02/15/2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and dependent claims rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1, Applicants have the limitation "prodrugs". What are the structures of these "prodrugs"? Applicants '"prodrugs" are molecules whose structure lie outside the subject matter of formula (I), but upon metabolism in the body are converted to active compounds falling within the structural scope of formula 1. The claim describes the function intended but provides no specific structural guidance to what constitutes a "prodrug". Structural formulas, names, or both can accurately describe organic compounds, which are the subject matter of claim 19. Attempting to define means by function is not proper when the means can be clearly expressed in terms that are more precise.

Likewise, the limitation 'solvates' is present without distinctly stating what the composition of the solvates is.

The redefinition of Ra, claim 1, second page, line 3 from the bottom, is confusing because the definition of R includes definition for Ra.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and dependent claims are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of compounds of the formula, does not reasonably provide enablement for the plurality of possible structures claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The specification is enabling for a limited number of

possibilities for the substituents R and X. The specification, *for example*, while enabling for making symmetrical disulfides such as the compound of claim 39, is not enabling for making unsymmetrical disulfides such as the one conceivable from cysteine. It is not seen, *for example*, where in the specification, enabling disclosure for making or using (biological activity) compounds wherein S(O)2-S(O)2- linkage is present. Further, it is not seen where enabling disclosure for prodrugs or solvates, is present in the specification for compounds of formula I; what is discussed is academic teachings about prodrugs.

The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the relevant factual considerations.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art.

All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of the claims: The elected group I is drawn to compounds of the following formula wherein the independently varying substituents (layered on top of substituents) are defined. These compounds encompass molecules that widely vary in the physical and chemical properties such as size, molecular weight, logP, acidity and basicity, properties that are known in the art to greatly influence the PK and PD parameters that are relevant for the use aspect of the claimed invention. Further, the claims are also drawn to prodrugs and solvates of undefined chemical structures rendering the breadth and scope of the claims large that is not supported by the disclosure in the specification.

The level of the skill in the art: The level of skill in the art is high. However, due to the unpredictability in the art of organic and medicinal chemistry, it is noted that each embodiment of the invention is required to be individually assessed for viability.

The amount of direction provided by the inventor and the presence or absence of working examples:

The disclosure with respect to making compounds is limited to making S-Alkyl and S-nitosyl, bonds. With regards to making disulfides and derivatives, the schemes present in the specification on page 65 for the formation and on page 63 are of academic nature. The working examples present in the specification is limited to symmetrical disulfides such as 2,2'-dithiodiisosorbide.

While methods for making S-C bond formation is well-known in the art, the of C-C bond formation is known in the art organic chemistry to be fraught with uncertainties, especially in stereospecific manner as required for compounds of formula I requiring the R* substitution. There is no direction or guidance or working example present in the specification for compounds wherein C-R* is C-H or C-C. Thus notwithstanding the statement on page 16, lines 3-6 of the specification, undue experiment would be needed to make such compounds.

It is unclear what is intended with respect to biological use of compound with S-acyl bonds. No biological activity relating to such compounds are disclosed. The in vivo hydrolysis of such compounds would provide the pharmacophore that is known in the teachings of Molliner et al. (Also see, for example, cited references for rejection under 35 U.S.C. 103, US 5665766 and US 6858632)

The definition of Ra (see also rejection under 35 U.S.C. 112 second paragraph), includes OH and halogen as possible variables. The structures corresponding to these are undisclosed and are not enabled in the specification. Further, the structural units relating to these possibilities, such as S-S-CH2-CH2-Br are uncommon in compounds of therapeutic value.

The guidance and direction provided in the specification are lacking to meet these uncertainties. For example, the specification does not provide citations (commercial or literature) for procuring the

starting materials usable that could substitute for the lack of working examples with respect to non-enabled substitutions.

The specification lacks guidance for making or using prodrugs (and solvates). See rejection under 35 U.S.C. 112, second paragraph. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo,* this is still an experimental science. It is well known in the art that for a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be biologically active. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large degree of experimentation. The disclosure relating to these tests is lacking in the specification.

The state and the predictability of the art: The state of the medicinal chemistry is unpredictable. While the biological activities some of the claimed but undisclosed compounds are predictable (See rejections under 35 U.S.C. 103), the therapeutic activities of many compounds need to be individually assessed. Many of the claimed substituents, such as alkylating agents, are of questionable use. The disclosure in the specification is limited to few structurally closely related compounds. The existence of such unpredictabilities and uncertainties would prevent one of ordinary skill in the art from accepting the enabling disclosure for a limited number of compounds of very similar structures, on its face as universally applicable for all the substitutions claimed.

The quantity of experimentation: For the reasons presented above, there is a substantial gap between

what is taught in the specification and what is being claimed. Thus, given that the specification discloses biological activity for limited number of narrowly defined variables coupled with the limited enabling chemistry, one skilled in the art of medicinal chemistry would be faced with undue experiment to make and use other specific embodiments encompassed by the formula that would provide desirable biological activity.

It is suggested that the terms 'prodrugs' and solvates are deleted from the claims.

It is suggested, limitations relating to C-C bonds discussed above relating to R*-isosorbides are deleted from the claims.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, one of ordinary skill in the art would have to engage in undue experimentation to make and use the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1 and dependent claims are rejected under 35 U.S.C. 103(a) as being obvious over Stoss (US 4891373), Byrne et al (US 5665766), Molliner et al. (US 6858632, WO 2000020420) and Nallet et al (WO/0303037).

The instant claims are drawn to isosorbide 5-mononitrate derivatives substituted at the 2-position wherein sulfur-isosorbide linkage is present at the 2-position.

The cited art prior art references are drawn to isosorbide 5-mononitrate derivatives substituted at the 2-position.

The difference with respect to compounds of Stoss, Byrne and Nallet is in the substitution at the 2-position. The prior art compounds do not have the sulfur-isosorbide linkage at the 2-postion, instead have oxygen-isosorbide linkage is present at the 2-position. Molliner et al. teach compounds wherein sulfur-isosorbide linkage is present at the 2-position, although, Molliner et al.s. compounds are different in their other substitution on the sulfur.

Prior art teaches that a wide variety of substitutions at the 2-position is tolerated for the retention of vasodialating properties of the derived compounds. Thus one skilled in the art at the time of the application engaged in the preparation of analogs of isosorbide 5-mononitrate would be motivated to modify the 2-position with sulfur analogs because Molliner et al teach sulfur analogs linked to the pharmacophoric isosorbide 5-mononitrate retain the vasodilating properties.

Claims 1-8 are rejected.

Allowable Subject Matter

Claim 39 is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NIZAL S. CHANDRAKUMAR whose telephone number is (571)272-6202. The examiner can normally be reached on 8.30 AM - 4.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571 0272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nizal S. Chandrakumar

/D. Margaret Seaman/

Primary Examiner, Art Unit 1625